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EDITORIAL

This is Why we do Randomised Trials!

Those who participated in the GALA (General vs Local Anaesthesia) Trial are to be congratulated, not only for having completed the largest ever randomised trial involving carotid endarterectomy (CEA), but also for having demanded that 'level I evidence' rather than 'intuitive reasoning' resolve a controversial issue in contemporary carotid surgical practice.[1] The final results may not be quite what the founders of this trial expected, but they can be comforted by the fact that they are not alone. The history of medicine is littered with examples of where the results of randomised trials prove contrary to 'expert opinion' and meta-analyses of non-randomised publications.

David Kent likened this phenomenon to the 'shimmer effect' where increasingly greater claims are made for a product/treatment, only for these to be rejected following critical scientific scrutiny.[2] In an editorial accompanying a paper suggesting that peri-operative statin usage reduced the risk of stroke during CEA, Kent reminded the reader of the increasing evidence (including meta-analyses[3]) that administering hormone replacement therapy (HRT) to post-menopausal women in order to reduce major cardiovascular events was so compelling that it might even be unethical to consider performing a randomised trial. Yet when such a trial was undertaken (the Heart and Estrogen–progestin Replacement Study (HERS)[4]), it showed that not only did HRT not reduce the cardiovascular risk, it actually increased the risk of thromboembolic events.

Closer to home, some prominent vascular surgeons were opposed to the need for performing randomised trials comparing CEA with 'best medical therapy' in patients with asymptomatic carotid disease. To them, the published evidence was similarly compelling. However, following publication of the Asymptomatic Carotid Atherosclerosis Study (ACAS) in 1995, respected voices in the vascular surgical community later admitted that, while ACAS had shown a small but significant benefit favouring CEA, the late stroke risk in patients randomised to medical therapy was very much less than had been anticipated from the preceding non-randomised, observational studies in the literature.[5] Similarly, large scale randomised trials have determined that outcomes following eversion CEA are no different to those following traditional CEA[6] (provided the latter involves patch closure of the arteriotomy site) and that routine patch closure is safer than a policy of routine primary closure.[7] These examples of Level I evidence are really important should vascular surgeons be challenged (medicolegally) regarding aspects of their carotid surgical practice. What a shame, therefore, that debate regarding the remaining 'titans' of carotid practice (routine *vs* selective patching/shunting) will never be resolved by randomised comparison.

If nothing else, GALA has reminded the surgical community of the fact that well conducted randomised trials provide much better quality evidence than observational studies that are inevitably prone to inherent biases. In this respect, readers are strongly recommended to read Bruce Campbell's excellent chapter on how data can be 'manipulated' in order to produce better outcomes.[8]

Only as recently as last week, the Cochrane Group published its 2008 systematic review of nine randomised trials (812 operations) comparing general and locoregional anaesthesia (excluding GALA) as well as outcomes from 47 non-randomised studies involving no fewer than 24,181 patients.[9] A meta-analysis of the randomised trials again showed no evidence that CEA under locoregional anaesthesia reduced the risk of procedural stroke. However, a systematic review of the non-randomised trials showed significant reductions in stroke (38/47 studies), death (42/47 studies), stroke or death (27/47 studies), myocardial infarction (27/47 studies) and pulmonary complications (7/47 studies). In the GALA trial (with 3526 randomised patients), none of these endpoints found any statistically significant association favouring locoregional anaesthesia (LRA).

The overall 30-day mortality rate in GALA was 1.5% in GA patients *vs* 1.1% in those randomised to LRA. The death/stroke rate was 4.6% (GA) *vs* 4.2% (LRA), while the 30-day risk of death/stroke and MI (the primary endpoint in this study) was 4.8% (GA) *vs* 4.5% (LRA). There were a number of other interesting analyses published in GALA. The rate of myocardial infarction was 0.2% where GA was used *vs* 0.5% for patients undergoing CEA with LRA. Given the prevailing opinion prior to GALA that surgery under LRA reduced peri-operative cardiac morbidity, this was a somewhat surprising

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finding. Similarly, there was no difference in quality of life, length of hospital stay or use of HDU/ITU facilities relative to choice of anaesthesia and no significant difference in endpoints in a series of prespecified subgroups (patients aged >75 years, patients scored as having increased surgical risk). Interestingly, there was a non-significant trend towards better outcomes in patients undergoing CEA under LRA if they had a contralateral occlusion (difficult to know how to interpret this given the small numbers involved), while the one-year survival rates were non-significantly higher in patients undergoing their CEA under LRA, an observation that is similarly hard to currently explain.

The GALA trial is, however, notable for what it has not revealed. Was there any difference in outcome in symptomatic *vs* asymptomatic patients? GALA claims that their surgical results represent an improvement on the earlier ECST and NASCET studies, but stratification for symptom status has not yet been released into the public domain. Similarly, we have not been provided with any information regarding the timing of procedure related strokes. The rationale underlying CEA under LRA is that it will accurately identify patients with inadequate collateralisation that then require shunting so as to reduce the risk of haemodynamic stroke. Accordingly, did patients randomised to LRA suffer fewer intra-operative strokes? Were there any patterns regarding the timing of post-operative strokes (some have postulated that general anaesthesia may increase a patient's thrombotic risk)? Finally, and of most practical importance to this observer, did CEA under LRA reduce the incidence and need for treatment for post-operative hypertension, a condition seen relatively commonly in patients undergoing CEA under general anaesthesia?

So how should these results be interpreted? First and foremost, surgeons may continue to perform CEA under general or locoregional anaesthesia (as to their preference) without fear of being criticised on the basis of evidence. As was succinctly stated by Pettiti,[10] ''experimentation trumps observation''. Second, it is reassuring to know that other than a slight prolongation of the operation time, CEA under LRA involving trainee surgeons and anaesthetists was not associated with any excess risk. Accordingly, surgeons/anaesthetists who are currently unfamiliar with LRA may now feel more confident about introducing this technique into their practice if they wish. Third, surgeons cannot be pressurised by managers and accountants in to performing CEA under LRA purely on the basis that this will reduce hospital costs through reduced ITU/HDU and overall length of hospital stay, as was implied in a number of non-randomised studies. Fourth, is the simple fact that surgeons must accept that if they wish to use a policy of selective shunting then they must start performing CEA under LRA. It is an indisputable fact that CEA under LRA will always be the 'gold standard' for identifying patients who definitely need a shunt. No other monitoring technique comes close in terms of accuracy and safety (or ever will) and this debate should really now be ended.

Will I be changing practice? No. I remain a committed 'routine shunter' and have never subscribed to the belief that shunts cause as many strokes as they prevent. It is my contention that there are many more important aspects for understanding and preventing procedural strokes.[11] I would, however, add one important caveat to this conclusion. If it can be shown that CEA under LRA reduces post-operative hypertension, I would definitely be more motivated to change an anaesthetic practice that has worked very well in this Institution. Come on GALA, give us this information!

Conflict of Interest

The authors have no conflict of interest.

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